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Serum and red blood cell folate levels in parturients, in the intervillous space of the placenta and in full-term newborns

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1 Introduction

Folates are essential nutrients for human beings and play a fundamental role in the metabolism of several amino acids and in the synthesis of nucleic acids. They are especially important during pregnancy when the demand for folates greatly increases, with a consequent tendency to drops in folate levels as pregnancy progresses [6, 13, 15].

It has been well established that serum and red blood cell folate concentrations are higher in full-term newborns than in their mothers [2, 5, 10, 14]. Some investigators have suggested that the placenta may concentrate folates, thus guaranteeing high concentrations of this vitamin to the fetus [4, 12]. Folate measurement in the intervillous space of the placenta would provide data on the amount of folate the fetus has at its disposal for uptake. To our knowledge, however, no reports on folate determination in this compartment have been published in the literature.

The objective of the present study was to determine and compare serum and red blood cell folate levels in the mother, in the intervillous space of the placenta and in the neonate born at term, in order to contribute to the elucidation of some as yet unexplained points related to folate metabolism in pregnant women and to folate transfer from mother to fetus.

Curriculum vitae

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2 Material and methods

The sample consisted of 51 parturients and their respective placentas and concepts. The parturients were patients admitted to the University Hospital of Porto Alegre, State of Rio Grande do Sul, Brazil, and were included in the study only after satisfying the following requirements with respect to the ongoing pregnancy: uneventful gestation of 38 to 42 weeks duration; uncomplicated vaginal delivery; newborns showing no abnormalities when examined clinically, weighing more than 2500 g and with an APGAR score of 7 or more during the 1st and 5th minute; no supplementation with folic

acid during pregnancy, and no intake of drugs acting on folate metabolism.

Blood was obtained from the parturients by vein puncture during or immediately after placental expulsion, after a fasting period of at least 3 hours. Blood was collected from the newborns by puncturing the umbilical vein (placental side) immediately after placental expulsion, and from the intervillous space of the placenta by puncturing the chorionic plate according to the technique of MEIRELLES and MATHEUS [8]. Part of the blood was left in a tube without anticoagulant, and the serum was removed and stored frozen at – 20 °C until the time for serum folate measurement. The remaining portion of the sample was placed in a tube with 10% EDTA and diluted with 1% ascorbic acid (1 : 21 v/v). The hemolysate was stored frozen at – 20 °C until the time for determination of red blood cell folate. Serum and red blood cell folate levels were measured by radioimmunoassay using commercial kits (Diagnostic Product Corporation). The results were analyzed statistically with a Burroughs B 6700 computer using SPSS programs (Statistical Package for the Social Sciences) [9]. Comparison between means was done employing Students's test for paired samples. PEARSON linear correlation coefficient was applied in order to estimate association between variables. The level of significance was set at 5%.

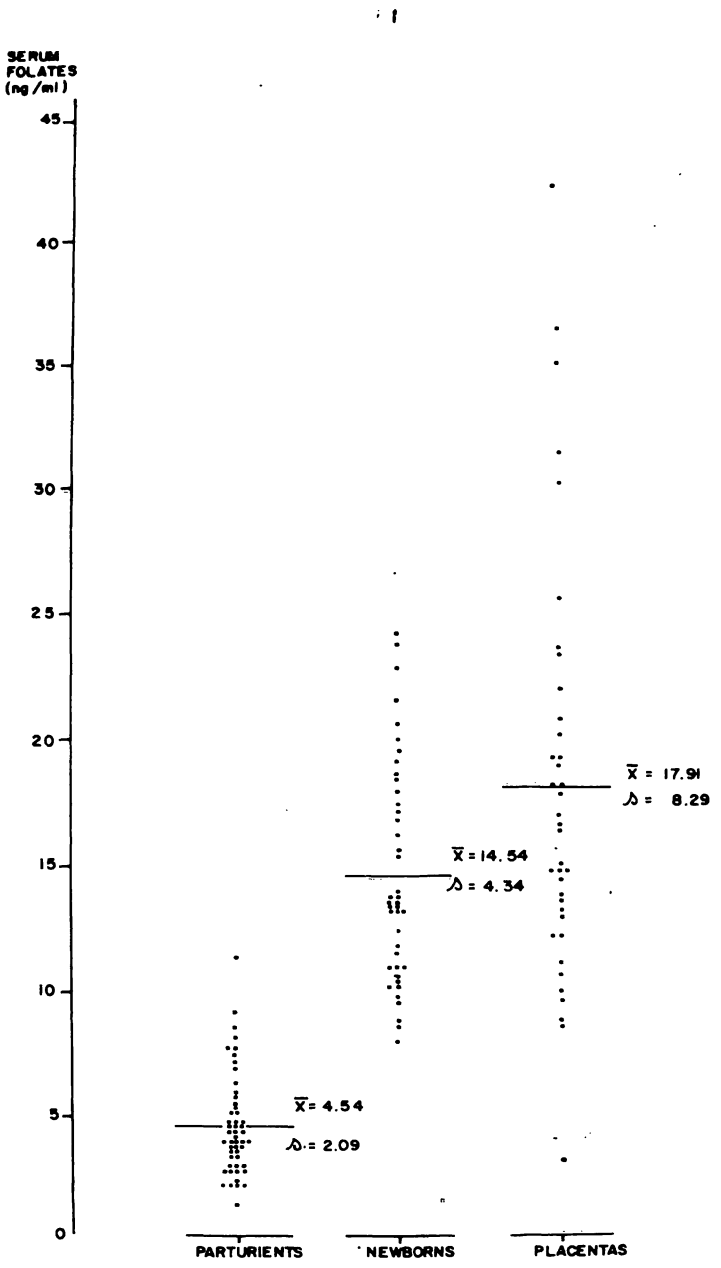

Fig. 1. Serum folate levels in parturients, newborns and placentas. The horizontal lines indicate the means.

3 Results

Figs. 1, 2 show the levels of serum and red blood cell folates in the parturients, placentas and concepts. Mean serum folate levels were significantly higher in newborns than in their mothers ($t = 16.08$, $P < 0.001$). Serum folate was higher in the newborns than in the mothers in all cases. Similarly, mean levels of red blood cell folates were significantly higher in the newborns than in their mothers ($t = 11.29$, $P < 0.001$). Only in 2 cases was the level of red blood cell folates lower in the newborns than in their mothers. A significant positive correlation occurred between mother and newborn folate levels in both serum and red blood cells.

Mean serum folate levels in the intervillous space of the placenta were significantly higher than in the parturients ($t = 10.6$, $P < 0.001$) and serum folate levels in this compartment were higher than maternal ones in all cases. Mean serum folate levels in the intervillous space were significantly higher than in the newborns ($t = 2.82$, $P < 0.01$). In 10 cases serum folate concentrations were higher in the umbilical cord than in the intervillous space of the placenta. Significant positive correlation occurred between placental and maternal serum folates, and between placental and neonatal serum levels. In turn, the mean levels of placental red

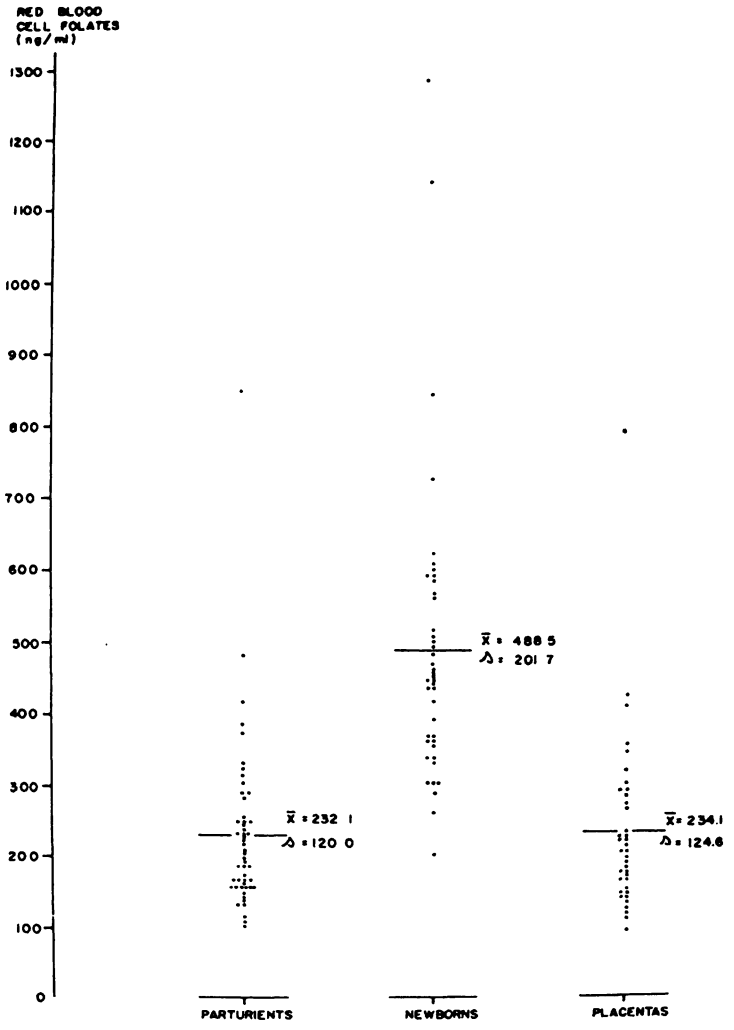

Fig. 2. Red blood cell folate levels in parturients, newborns and placentas. The horizontal lines indicate the means.

blood cell folates were similar to the maternal ones ($t = 1.18$, $P > 0.05$), with a strong positive correlation between them. A significant positive correlation was detected between serum folate levels and red blood cell folate levels in the mothers and in the newborns. Tab. 1 shows the results of the correlations calculated in the present study.

4 Discussion

Several studies have shown that serum and red blood cell folate levels in full-term newborns are higher than in their mothers [2, 5, 10, 14], and these observations were confirmed in the present investigation. This fact suggests the presence of a mechanism that guarantees adequate amounts of this vitamin to the fetus. STRELLING [12] suggested that the placenta may function effectively in transferring folates to the fetus for the fetus's benefit. The folate levels detected in the present study in the intervillous space of the placenta support this suggestion and contribute to the hypothesis advanced by some investigators that the placenta may concentrate folates [4, 12]. ANTHONY et al. [1] isolated a specific folate-binding protein from the placenta. Since the so-called specific folate-binding proteins are believed to have the function of binding folates for storage [11], their presence in the placenta may account for the folate concentrations observed in this organ.

It has long been believed that the fetus removes folates from a compartment having lower concentrations of this vitamin that the fetus's own levels. The results of the present study show that, most of the time, the fetus actually withdraws folates from a compartment with high folate levels, since mean serum folate levels in the intervillous space of the placenta were significantly higher than in the newborn. Otherwise stated, the newborn has high serum folate levels in relation to its mother because high folate concentrations are offered to it. The fact that in some cases serum folate levels were higher in the newborn than in the intervillous space suggests that, in addition to folate concentration by the placenta, other mechanisms may be

Tab. I. Correlation coefficients (r) and significance (P) of the correlations between different variables.

Variables			r	P
Maternal serum folates	X	Neonatal serum folates	0.361	< 0.01
Maternal red blood cell folates	X	Neonatal red blood cell folates	0.365	< 0.01
Maternal serum folates	X	Placental serum folates	0.407	< 0.01
Neonatal serum folates	X	Placental serum folates	0.368	< 0.05
Maternal red blood cell folates	X	Placental red blood cell folates	0.942	< 0.001
Maternal serum folates	X	Maternal red blood cell folates	0.563	< 0.001
Neonatal serum folates	X	Neonatal red blood cell folates	0.379	< 0.01

involved in folate transfer to the fetus, thus permitting the fetus to build up higher folate concentrations than offered to it.

Although a mechanism exists which undoubtedly favors the fetus, the folate concentrations in the newborn are related to those in the placenta and these, in turn, to those of the mother, since positive correlation was observed between them.

The fact that the levels of red blood cell folates in the intervillous space of the placenta were, on the average, almost identical to those in the mother and the fact that the correlation coefficient between them was close to one indicate that the erythrocytes suffer no alterations in terms of their folate stores when circulating in the intervillous space of the placenta.

Positive correlation has been reported between serum and red blood cell folate concentrations [2, 3, 5, 7] and the results obtained in the present paper confirm these observations. Thus, the correlation existing between the red blood cell folate levels in mothers and newborns may simply be the consequence of the correlation between serum folate levels in the mother-newborn binomium.

Summary

Folates, essential nutrients for man, are especially important during gestation. Serum and red blood cell folate levels were measured in 51 parturients and in their respective placentas and concepts, with the objective to further elucidate the mechanisms of folate transfer from mother to fetus. The interrelationships between the three compartments with respect to folate levels were also studied (Tab. I). Serum and red blood cell folates were measured by radioimmunoassay in samples of venous blood from the mother, from the intervillous space of the placenta, and from the umbilical cord. Higher folate levels were detected in newborns than in their mothers both in serum (3.9 times) and red blood cells (2.3 times). Serum folate levels were higher in the intervillous space of the placenta than in newborns (1.3 times) or mothers (4.5 times) Fig. 1, 2). These data suggest that the placenta concentrates folates, thus offering high concentrations of this vitamin to the fetus. It is possible that folate-binding proteins existing in the placenta participate in the mechanism of folate concentration in this organ. However, despite the existence of a transfer mechanism that benefits the fetus, a significant positive correlation was observed between serum folate levels of mothers, newborns and placentas.

Keywords: Folates, maternal-placental-fetal exchanges, placental transfer.

Zusammenfassung

Folsäurespiegel im Serum und in Erythrozyten bei Gebärenden, in den intervillösen plazentaren Räumen und bei reifen Neugeborenen

Folsäuren sind als essentielle Bausteine der menschlichen Ernährung während der Schwangerschaft von besonderer Wichtigkeit. Mit dem Ziel, Erkenntnisse über den Mechanismus des Folsäuretransportes von der Mutter zum Feten zu gewinnen, haben wir die Folatspiegel im Serum und in den Erythrozyten bei 51 Gebärenden und deren Plazenten bzw. Neugeborenen bestimmt. Dabei wurden auch die Beziehungen zwischen den 3 Kompartimenten bezüglich des Folsäurespiegels untersucht (Tab. I). Wir bestimmten die Serum- und Erythrozyten-Folsäurespiegel mit einem Radioimmunoassay in venösen Blutproben von der Mutter, aus den intervillösen Räumen der Plazenta und aus der Nabelschnur. Dabei waren die Folatspiegel der Neugeborenen sowohl im Serum (Faktor 3,9) als auch in den Erythrozyten (Faktor 2,3) gegenüber dem mütterlichen Blut erhöht. Im intervillösen Raum wurden höhere Folatspiegel gemessen als bei den Neugeborenen (Faktor 1,3) und bei den Müttern (Faktor 4,5) (Fig. 1, 2). Diese Ergebnisse lassen vermuten, daß die Plazenta Folsäure konzentriert und auf diesem Weg dem Feten ein hohes Angebot bereitstellt. Möglicherweise gibt es in der Plazenta Proteine, die Folsäure binden und so an der Folatkonzentration in diesem Organ beteiligt sind. Neben diesem spezifischen Transportmechanismus, von dem der Fet profitiert, gibt es jedoch auch eine signifikante, positive Korrelation zwischen dem Serum-Folsäurespiegel bei der Mutter, beim Neugeborenen und in der Plazenta.

Schlüsselwörter: Folsäure, materno-fetaler plazentarer Austausch, plazentarer Transfer.

Resumé

Taux sériques et globulaires de folates chez les parturientes, dans la chambre intervilleuse placentaire et chez les nouveaux-nés à terme

Les folates, nutriments essentiels pour l'homme, sont particulièrement importants au cours de la gestation. Pour mieux comprendre les mécanismes de transfer des folates de la mère au fœtus, les taux sériques et érythrocytaires de cette vitamine ont été dosés chez 51 parturientes au niveau de leurs placentas et chez leurs enfants On a étudié aussi les interrélations entre les 3 compartiments

(Tab. I). Les folates sériques et érythrocytaires du sang veineux de la mère, de l'espace intervillositaire et du cordon ombilical ont été dosés par méthode radioimmunologique. Les résultats ont montré des taux plus élevés chez le nouveau-né que chez la mère, que ce soit pour les folates sériques (3,9 fois) ou que ce soit pour les folates érythrocytaires (2,3 fois). Les taux des folates sériques sont plus élevés dans l'espace intervillositaire que chez le nouveau-né (1,3 fois) et chez la mère (4,5 fois) (Figs. 1 et 2). Ces données suggèrent que le placenta concentre les folates, offrant ainsi au fœtus de hautes concentrations de cette vitamine. Il est possible que l'existence de protéines liées aux folates dans le placenta prenne part au mécanisme de concentration des folates dans cet organe. Cependant, malgré l'existence d'un mécanisme de transfert qui bénéficie au fœtus, on a observé une corrélation positive significative entre les taux des folates maternels, néonataux et placentaires.

Mots-clés: Folates, échanges materno-placento-fœtales, transport placentaire.

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Bibliography

[1] ANTHONY, A. C., C. UTLEY, K. C. VAN HORNE et al.: Isolation and characterization of a folate receptor from human placenta. J. Biol. Chem. 256 (1981) 9684

[2] EK, J., E. M. MAGNUS: Plasma and red blood cell folate during normal pregnancies. Acta Obstet. Gynecol. Scand. 60 (1981) 247

[3] HOFFBRAND, A. V., B. F. A. NEWCOMBE, D. L. MOLLIN: Method of assay of red cell folate activity and the value of the assay as a test for folate deficiency. J. Clin. Pathol. 19 (1966) 17

[4] LANDON, M. J., D. H. EYRE, F. E. HYTTEN: Transfer of folate to the fetus. Br. J. Obstet. Gynaecol. 82 (1975) 12

[5] LORÍA, A., L. SANCHEZ-MEDAL, J. LABARDINI et al.: Comparación entre el estado nutricional de la madre e del recien nacido. Gac. Med. Mex. 99 (1969) 229

[6] MARTIN, J. D., R. E. DAVIS: Serum folic activity and vaginal bleeding in early pregnancy. J. Obstet. Gynaecol. Br. Cwlth. 71 (1964) 400

[7] MARTINEZ, O. B.: Red cell folate values of a group of non pregnant mothers. Can. J. Publ. Health 71 (1980) 163

[8] MEIRELLES, R. S., M. MATHEUS: Método para obtenção do sangue no espaço interviloso da placenta humana. Obst. Ginec. Lat. Am. 30 (1972) 238

[9] NIE, N. H., C. H. HULL, J. G. JENKINS et al.: SPSS; Statistical package for the social sciences. 2nd ed., McGraw-Hill Book Co., New York 1975

[10] RAMON, D. M., C. J. ELIZONDO, V. F. RODRIGUEZ: Niveles sericos de hierro y niveles sericos e intraeritrociticos de folatos en la sangre materna y de cordon. Rev. Invest. Clin. (Mex.) 29 (1977) 195

[11] RUBINOFF, M., R. ABRAMSON, C. SCHREIBER et al.: Effect of a folate-binding protein on the plasma transport and tissue distribution of folic acid. Acta Haematol. 65 (1981) 145

[12] STRELLING, M. K.: Transfer of folate to the fetus. Dev. Med. Child Neurol. 18 (1976) 533

[13] VAZ PINTO, A., F. SANTOS, A. M. ALMEIDA et al.: Trends of folate and vitamin B_{12} during pregnancy. Rev. Invest. Clin. 25 (1973a) 153

[14] VAZ PINTO, A., F. SANTOS, M. C. MIDLEJ et al.: Vitamin B_{12} and folic acid in maternal and newborn sera. Rev. Invest. Clin. 25 (1973b) 341

[15] WILLOUGHBY, M. L. N., F. G. JEWELL: Folate status throughout pregnancy and in postpartum period. Br. Med. J. 4 (1968) 356

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Timing of Aneurysm Surgery

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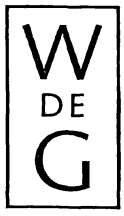
The most recent analyses of the results obtained when a series of patients with subarachnoid hemorrhage from a ruptured cerebral aneurysm were operated on within the first three days of bleeding are compiled in this volume. In order to arrive at a clearer concept of the effect of timing, these data are compared with the results obtained when patients were operated on at a later stage. New pharmacological approaches that may prevent symptomatic vasospasm, one of the major complications following subarachnoid hemorrhage, are presented. Since the combination of radical surgery and pharmacological prevention of symptomatic vasospasm with calcium antagonists seems to improve the chances of successful treatment, the following topics are discussed: new requirements of transportation in the acute stage and the availability of radiology and anesthesiology as well as a neurosurgical team for treatment in the acute stage.

Topics:
Diagnosis · Technical aspects of surgical treatment · Timing of operation, surgical results and follow-up results · Prevention and/or treatment of delayed ischemic deficit from vasospasm · The problem of organising acute operation



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